REMARKS

Claims 1-8 stand rejected, and claims 9-22 stand withdrawn. Applicants have amended claim 1 herein to recite a transgenic mouse or rat, the nucleated cells of which comprise a transgene comprising an immunoglobulin kappa light chain 3' enhancer sequence operably linked to a nucleic acid sequence encoding an anti-apoptotic polypeptide in the Bcl-2 family, wherein the transgenic mouse or rat exhibits expanded plasma cell and mature B cell populations as compared with a corresponding wild-type mouse or rat. Applicants also have amended claims 2-6 and 8 for consistency with claim 1. Support for these amendments can be found throughout the specification as filed, including in the Examples. In addition, Applicants have added new claims 23-29. Claim 23 recites a transgenic rabbit, the nucleated cells of which comprise a transgene comprising an immunoglobulin kappa light chain 3' enhancer sequence operably linked to a nucleic acid sequence encoding an anti-apoptotic polypeptide in the Bcl-2 family, wherein the transgenic rabbit exhibits expanded plasma cell and mature B cell populations as compared with a corresponding wild-type rabbit. Claims 24-29 are analogous to claims 3-8. Support for claims 23-29 can be found in Applicants' specification at, for example, page 4, lines 24-29. Thus, no new matter has been added.

In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 1-8 and 23-29.

Rejection under 35 U.S.C. § 112

The Examiner rejected claims 1 and 3-8 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. In particular, the Examiner alleged that the specification did not reasonably provide enablement for claims broadly drawn to transgenic rodents, or cells derived from a transgenic rodent.

Applicants respectfully disagree. The previous claims were fully enabled. To further prosecution, however, Applicants have amended the present claims to recite a transgenic mouse or rat. As stated by the Examiner at page 2 of the Office Action, the specification is enabling for a transgenic mouse whose genome comprises a transgene as recited in the present claims. Applicants submit that the specification also is enabling for a transgenic rat, as well as a

transgenic rabbit. The proper standard for enablement is that the specification teach those of skill in the art how to make and use the invention without "undue experimentation." M.P.E.P. § 2164.01. As stated by the Federal Circuit, "a considerable amount of experimentation is permissible if . . . the specification in question provides a reasonable amount of guidance with respect to the direction in which the experiment should proceed." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Applicants' disclosure satisfies this requirement.

Applicants' specification provides ample and detailed guidance for generating transgenic animals as recited in the present claims. For example, Applicants' specification teaches how to make a transgene construct containing an immunoglobulin kappa light chain 3' enhancer sequence operably linked to a nucleic acid sequence encoding an anti-apoptotic polypeptide in the Bcl-2 family, as recited in the present claims. *See*, e.g., page 5, line 16 to page 6, line 24. Applicants' specification also teaches how to generate a transgenic non-human animal (e.g., a mouse , rat, or rabbit) via, for example, embryo microinjection, retrovirus-mediated gene transfer, gene targeting into embryonic stem cells, embryo electroporation, and *in vitro* transformation of somatic cells followed by nuclear transplantation. *See*, e.g., page 6, line 25 to page 7, line 9.

Further, at the time of Applicants' priority date, methods for generating transgenic animals such as mice, rats, and rabbits were widely available. *See*, for example, the Wall reference ((1996) *Theriogenology* 45:57-68; cited by Examiner), which discloses that the efficiency of integration for microinjected transgenes is similar for mice, rats, and rabbits (first full paragraph at page 61). Applicants note that transgenic mice as recited in the present claims were generated by pronuclear injection. *See*, Example 1 at pages 11 and 12 of Applicants' specification. Applicants further direct the Examiner to the Murakami et al. reference ((2002) *Theriogenology* 57:2237-2245; copy attached hereto), which discloses methods for generating transgenic rabbits.

In addition, those of skill in the art at the time of Applicants' priority date would have been aware of the similarities between Ig kappa light chain enhancers from different species. In particular, a skilled artisan would have recognized that the kappa enhancer sequence is highly conserved across mammalian species. *See*, e.g., the Emorine et al. reference ((1983) *Nature*

304:447-449; copy attached hereto). The similarities would have been further evident to a person of ordinary skill in the art because cell lines and transgenic animals expressing mouse and rat kappa immunoglobulin genes or gene fragments had been used for antibody production. *See*, e.g., the Schröeder et al. and Meyer et al. references (Schröeder et al. (1980) *Immunogenetics* 10:125-131; and Meyer et al. (1990) *Nucleic Acids Research* 18:5609-5615; copies attached hereto).

Thus, given the knowledge in the art at the time of Applicants' priority date, in combination with the fact that Applicants successfully generated transgenic mice as recited in the present claims, no undue experimentation would have been required for a person of skill in the art at the time of Applicants' priority date to make and use transgenic mice, rats, and rabbits as recited in the present claims. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1 and 3-8 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 1-7 as allegedly being unpatentable under 35 U.S.C. § 103(a) over the Grillot et al. reference (*J. Exp. Med.*, (1996) 183:381-391) in view of the Adams et al. reference (*Nature*, (1985) 318:533-538). In particular, the Examiner alleged that replacing the Ig heavy chain enhancer with the Ig light chain (kappa) enhancer taught by Adams et al. was nothing more than a simple substitution of one known element for another to obtain predictable results.

Applicants respectfully disagree. The standard for determining obviousness was articulated by the Supreme Court in *KSR Int'l. v. Teleflex Inc.* (127 S. Ct. 1727, 82 USPQ2d 1385 (2007)). "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741, 82 USPQ2d 1396. Rather, the Examiner must show an apparent reason to combine the known elements as claimed in the application being examined. *Id.* "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.* (*quoting In re Kahn*, 441 F.3d 997, 988 (Fed. Cir. 2006)); M.P.E.P. §2142.

In the instant application, the Examiner has based the rejection on the conclusion that Adams et al. found that the Ig light chain (kappa) enhancer and heavy chain (mu) enhancer function similarly in directing B cell specific expression of heterologous nucleic acids in transgenic mice. The Adams et al. reference, however, does not support this conclusion. For example, the Adams et al. reference reports that the heavy chain construct showed striking efficacy for causing aggressive lymphoma, leading the investigators to focus primarily on the E_μ – *myc* transgenic mice (*see*, e.g., page 534, right column, first full paragraph). Further, the Adams et al. reference disclosed that expression of the heavy chain enhancer-myc construct resulted in higher tumor incidence than observed with the light chain enhancer-myc construct (13/15 versus 6/17), as well as shorter latent periods (*see*, e.g., page 537, left column, first full paragraph). Adams et al. conclude that this observation "might reflect the greater enhancer activity of E_μ (the heavy chain enhancer) over E_κ (the light chain enhancer) with certain promoters, or a larger pool of susceptible cells, since E_μ is probably activated earlier in lymphoid ontogeny than E_κ." *Id.* at 537. Therefore, the Adams et al. reference indicates that the Ig kappa chain enhancer does not function similarly to the Ig heavy chain enhancer. Moreover, the Grillot et al. reference does not suggest using the Ig kappa chain enhancer. Thus, a person of ordinary skill in the art, reading the Adams et al. and Grillot et al. references, would not have been motivated to substitute the light chain enhancer of Adams et al. for the heavy chain enhancer of the Grillot et al. construct. As such, the combination of cited references does not render the present claims obvious.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1-7 under 35 U.S.C. § 103(a).

The Examiner rejected claim 8 as allegedly being unpatentable under 35 U.S.C. § 103(a) over the Grillot et al. reference in view of the Adams et al. reference, and further in view of the Miller et al. reference (*Immunogenetics*, (1992) 35:24-32). Specifically, the Examiner alleged that it would have been obvious to substitute the Ig kappa promoter from the construct of Miller et al. for the SV40 promoter of the Grillot et al. construct featuring the Adams et al. light chain enhancer.

Applicants respectfully disagree. As discussed above, Adams et al. demonstrated differences in function of the heavy chain enhancer and the light chain enhancer, and the Grillot et al. reference does not suggest using the Ig kappa chain enhancer. Thus, a person of ordinary skill in the art, reading the Adams et al. and Grillot et al. references, would not have been motivated to substitute the light chain enhancer of Adams et al. for the heavy chain enhancer of the Grillot et al. construct. The Miller et al. reference fails to suggest substituting the light chain enhancer for the heavy chain enhancer in the Grillot et al. construct, and thus it does not remedy the deficiencies of the Grillot et al. and Adams et al. references, as it. As such, a person of ordinary skill in the art at the time Applicants filed would not have been motivated to combine the teachings of the Grillot et al., Adams et al., and Miller et al. references. Accordingly the present claims are not obvious over the combination of cited references.

In light of the above, Applicants respectfully request withdrawal of the rejection of claim 8 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants submit that claims 1-8 and 23-29 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please charge $245 for the Petition for Extension of Time fees and apply any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

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